細胞死を起点とする

生体制御ネットワークの解明

領域番号：3601

平成２６年度～平成３１年度
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「新学術領域研究（研究領域提案型)」
研究成果報告書

令和２年６月

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はしがき

本領域は2014年に、細胞死に伴って起こる生体応答の解明を目的として、発足した。それまでの細胞死研究は、細胞死がどのようにして起こるかというメカニズムの解明に主眼が置かれ、細胞死が起きた後に、どのような生体応答が起きるのか、についての解析はほとんど進んでいなかった。死にゆく細胞が周囲の細胞にメッセージを発信し、生体応答を制御していることが明らかになりつつ状況を踏まえて、本研究領域では、そのメッセージの同定と生体内での意義を明らかにし、細胞死後の生体応答の包括的な理解に向けて研究を進めた。

本領域では、細胞死のみならず、免疫、炎症、修復、再生、ヒト遺伝性疾患を専門とする研究者と、オミックス解析や分子イメージングの専門家が一同に介し、これら研究者間の有機的連携により細胞死研究の発展を目指した。その結果、５年の研究期間に多くの共同研究が行われ、個別の研究では到達できない大きな成果がいくつも創出された。具体的には、複数の細胞死様式のイメージング技術の開発、遺伝性疾患における細胞死様式の意義の解明、ダイイングコードの同定とその生理的、病理的意義の解明等で、先駆的で、かつ今後の発展が期待できる研究成果が生まれた。本領域では、海外の細胞死関連の研究者との交流も積極的に行い、特にオーストラリアの細胞死研究者との緊密な連携ができたことは、日本の細胞死研究者にとって大きな財産となった。また、若手会議の開催等を通じて、次代を担う研究者の育成にも力を入れた。今後、本領域で醸成された研究者のコミュニティーがより発展し、細胞死研究に留まらない、新たな研究領域の創出、発展がなされることを期待する。

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	合計	直接経費	間接経費
2014 年度	214,890 千円	165,300 千円	49,590 千円
2015 年度	277,830 千円	213,720 千円	64,110 千円
2016 年度	272,870 千円	209,900 千円	62,970 千円
2017 年度	278,330 千円	214,100 千円	64,230 千円
2018 年度	272,870 千円	209,900 千円	62,970 千円
2019 年度	3,900 千円	3,000 千円	900 千円
総計	1,320,690 千円	1,015,920 千円	304,770 千円

研究発表

2018 年

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A01 公募研究

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A01　計画研究

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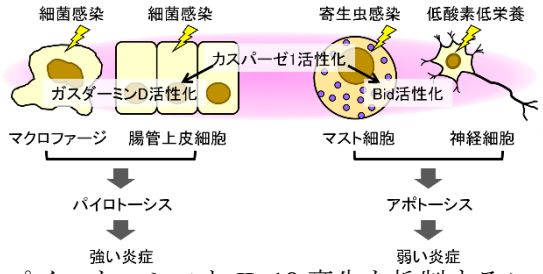
研究成果

A01 多様な細胞死の分子機構と生体内での捕捉

須田班

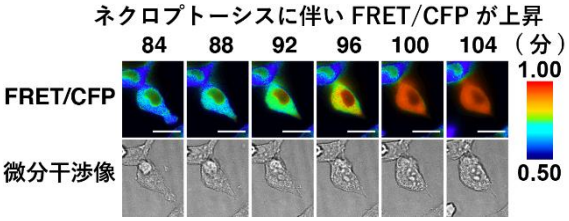


•カスパーゼ 1 の活性化はマクロファージや腸管上皮細胞などガスダーミン D を発現する細胞ではパイロトーシスを誘導するが、ガスダーミン D をあまり発現しない神経細胞やマスト細胞では Bid 依存性アポトーシスを誘導することを、計画班の山口らとともに明らかにした (Nat Commun 2019)。

•ビタミン B6 は NF-κB の活性化と NLRP3 インフラマソームの活性化を阻害し、細菌感染などによるマクロファージのパイロトーシスと IL-1β 産生を抑制すること、致死性エンドトキシンショックの動物モデルにおいて、ビタミン B6 の前投与によりマウスの生存率が改善することを見出した（J Biol Chem 2016）。

中野班 (大村谷)

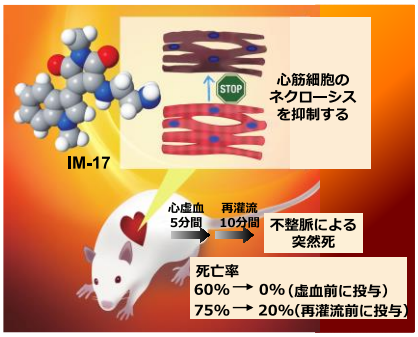
•胎児期から小腸上皮細胞でネクロプトーシスが誘導されるマウスを樹立し、3 型自然リンパ球が著明に活性化された結果、二次的にアポトーシスが小腸上皮細胞に誘導され、胎生致死となることを明らかにした（iScience 2019）。



•計画班の山口および公募班の白崎らとともに FRET の原理を利用して、SMART と命名したネクロプトーシスを特異的にモニタリングできる FRET バイオセンサーを開発し、さらに 1 細胞レベルで DAMPs の放出を可視化することに成功した (Nat Commun 2018)。

•計画班の田中（正）、田中（稔）らと共同して、肝死細胞の貪食に関与する食細胞を検討し、肝臓に常在するクッパー細胞ではなく、骨髄由来の単球であることを明らかにした。また肝死細胞から放出される DAMPs としてヒストン H3 を同定し、血管内皮障害に関与することを明らかにした（Hepatology 2017）。

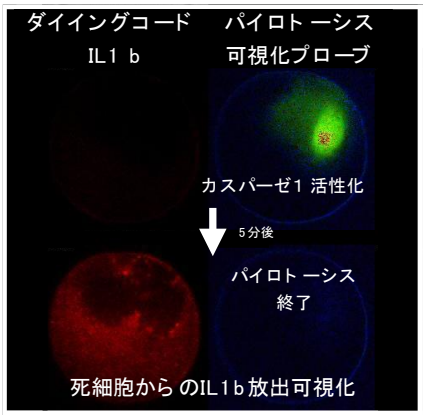
袖岡班 (闡闡)



•当初より目標として設定していた、酸化ストレスにより誘導されるネクローシスの抑制剤 IM 化合物の細胞死抑制剤としての基本的な特性の解明、動物実験に適用可能な誘導体 IM-17 の開発、さらには虚血心疾患モデルでの心筋保護作用に関して報告した(ACS Med Chem Lett 2018)。

•さらに IM 化合物に関して、その母核となる構造を変換した IL 誘導体を種々合成し、IM 化合物よりも数倍活性の高い誘導体を開発することにも成功した(Chem Pharm Bull 2016)。

•IM-17 をより高活性にした誘導体 IM-93 の開発にも成功し、計画研究班員の田中（正）、須田らとともに NETosis や Pyroptosis に対する効果も検討し、そのプロファイルを明らかにすることに成功した（ACS Med Chem Lett 2019）。



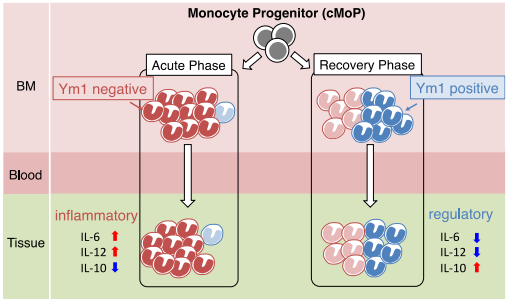
山口班 (荒川) •A20 はその脱ユビキチン化活性ではなく Znf7 domain 依存的にマクロファージで生じるネクロプトーシスを抑制することで、関節リウマチの発症を抑制することを公募班の白崎らと見出した(Nat Cell Biol 2019)。

•オートファジー依存性細胞死が胚発生および病態に関与することを明らかにした (Cell Death Differ 2017, Sci Signal 2018)。

•パイロトーシスをイメージングする FRET プローブ(SCAT1)およびその発現マウスを開発し、パイロトーシスに伴いダイングコード IL-1βがデジタルモードで放出されることを公募班の白崎らと解明した (Cell Rep 2014)。

A02　細胞死を起点とする生体応答とその異常

田中正班

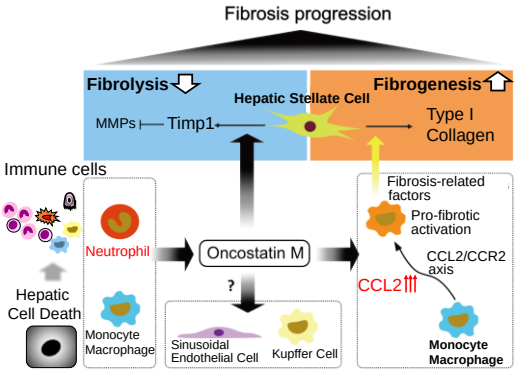


•計画班・分担研究者の大村谷と、組織傷害の回復期に骨髄で産生され、炎症の抑制や死細胞の貪食や組織修復に関与する新規単球サブセットの同定に成功した(Sci Immunol 2018)。

•計画班の袖岡、計画班・分担研究者の荒川と好中球のネトーシスとそれに伴う NET 形成に細胞内脂質酸化が関与していることを発見した (Sci Rep 2017) 。

•腸管の粘膜下層に局在する CD169 陽性マクロファージサブセットが、死細胞から放出される分子を認識して CCL8 を産生、放出することにより、炎症を惹起する働きがあることを発見した (Nat Commun 2015)。

田中稔班

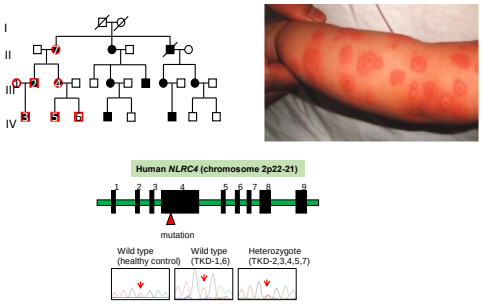


•Oncostatin M（OSM）が強力な肝線維化促進作用を有することを見出し、その機序として、単球・マクロファージに対しては線維促進性活性化を促す一方で、肝星細胞に対しては Timp1 を誘導し MMP による線維溶解を阻害していることを明らかにした。(Hepatology 2018)。

•計画班・分担研究者の大村谷らと、肝前駆細胞（LPC）の新規マーカー分子として同定した Lutheran は、肝障害の種類に応じて発現変動することでインテグリンシグナルを調節し、肝リモデリングを制御していることを明らかにした (Elife 2018)。

•計画班の中野、公募班の今井らと、非アルコール性脂肪性肝炎（NASH）発症の引き金となる肝細胞死にフェロトーシスが関与することを世界で初めて明らかにした（Cell Death Dis in press）。

安友班

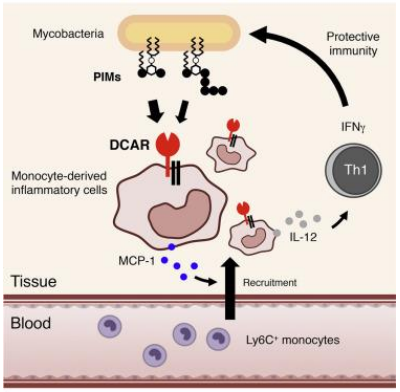


•計画班員の中野、山崎らと、小腸に存在する上皮間リンパ球の TCRαβ^{+}CD8αα^{+} T cells は Notch シグナルを受容することで Atp8a2 の発現を調節していることを見出した(PLoS Biol 2019)。

•家族性寒冷蕁麻疹の原因遺伝子として NLRC4 変異を同定し、NLRC4 変異により過剰なパイロプトーシスとサイトカイン放出が病気の原因であることを発見した (J Exp Med 2014)。

•肺線維症の原因遺伝子を同定して、同変異を持つマウスを樹立した。モデルマウスでも肺線維症を自然発症し、マウスモデルの解析から 2 型肺胞上皮細胞の necroptosis の亢進が初期病態であることを見出した(論文投稿中)。

山崎班 (宮本)



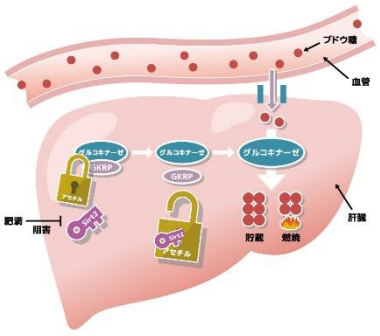
•死細胞上清中から新たな Mincle リガンドとして、ゴーシェ病原因糖脂質である β-glucosylceramide(β-GlcCer)を同定した（PNAS 2017）。

•計画班分担者の大村谷との共同研究により、カルジオリピンを認識する新たな C 型レクチン受容体として DCAR（dendritic cell immunoactivating receptor）を同定し、この受容体が、他のファミリー分子と異なり、単球由来炎症性細胞に限局して発現していること、結核菌特有の糖含有リン脂質（phosphatidyl-inositol mannoside）を認識し、免疫応答を活性化することを見出した (Immunity 2016)。

【公募研究】

A01 多様な細胞死の分子機構と生体内での捕捉

井上*班*



•脂肪肝における糖取り込み抑制機構は、肝細胞死・肝障害誘導に重要な役割を果たしているが、その肝糖取り込み抑制メカニズムに、Sirt2/GKRP が重要な役割を果たすことを見出した (Nat Commun 2018)。

山本班

•インターフェロン誘導性 GTPase の活性調節は、パイロトーシスの制御に重要である。オートファジー関連分子である LC3 ではなく GABARAP サブファミリー分子によるインターフェロン誘導性 GTPase の細胞内局在の制御が、その免疫応答に必須であることを明らかにした (Nat Immunol 2017)。

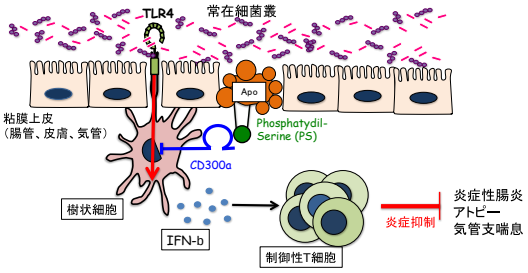
今井班

•タバコの煙をマウスに吸わせるとフェロトーシスを介した肺気腫が誘導されるが、GPx 4 トランスジェニックマウスでは抑制できる。またヒト COPD 患者肺上皮細胞でも GPx 4 の発現低下、NCOA4 の誘導、鉄の沈着と脂質酸化の亢進が見られ、フェロトーシスが発症メカニズムに重要な役割を担っていることが明らかとなった (Nat Commun 2019)。

瀬川*班*

•リン脂質フリッパーゼである ATP11C 欠損マウスで見られる B 細胞欠損症のメカニズムを解明した (PNAS 2018)。貪食受容体である MerTK/Axl と、そのリガンドである Gas6 や Protein S との結合の生化学的な特性を明らかにした。又、PtdSer 受容体である Tim4 が MerTK/Axl とリガンドの結合効率を大きく促進することを見出した (PNAS 2017)。

A02　細胞死を起点とする生体応答とその異常



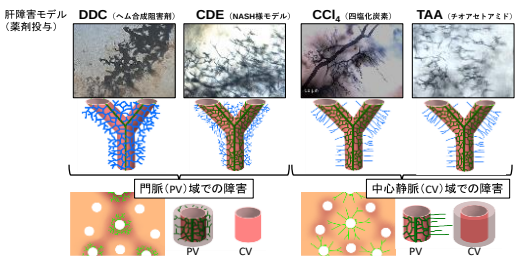
渋谷*班*

•腸管、皮膚、気道上皮細胞の死細胞表面上のホスファチジルセリンが樹状細胞状の CD300a と結合し、樹状細胞状からの IFN-βの産生を抑制することによって制御性 T 細胞の増殖の制御をすることを明らかにした (Nat Immunol 2016)。

植松*班*

•腹部への放射線照射では、陰窩細胞死に伴って遊離した ATP が、筋線維芽細胞に CCL11 を発現させ、好酸球を遊走させること、および、活性化筋線維芽細胞は、GM-CSF も産生し、それにより活性化した好酸球が、TGF-β を産生して筋線維芽細胞による線維化を促進することを見いだした。(Sci Transl Med 2018)。

伊藤*班*



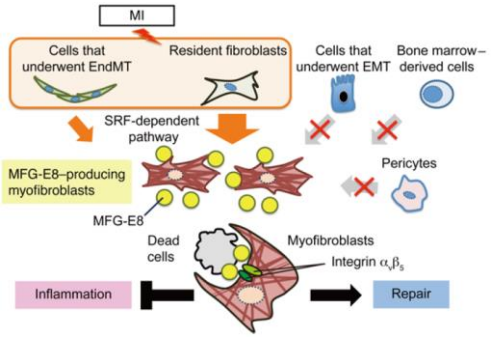
•独自に開発した 3 次元組織構造解析手法を用いて、マウス肝内胆管の微細構造を初めて明らかにした。さらに、病態の異なる種々の肝障害モデルでの比較解析により、従来「肝幹/前駆細胞の活性化」とされている現象の実態が『肝障害の病態に応じた、肝内の胆管上皮組織構造の適応的リモデリング』であることを明らかにした (Hepatology 2015)。

久本*班*

•神経切断によりカスパーゼが ABC トランスポーターの C 末端を切断してこれを活性化すると、ダイイングコード因子の一つであるホスファチジルセリンが切断軸索先端から放出される。それがホスファチジルセリン結合タンパク質 TTR-11 を介してインテグリンを活性化することで、切断神経の軸索再生が誘導されることを明らかにした (Nat Commun 2018)。

仲矢*班*

•心筋梗塞時の死細胞の貪食を MFG-E8 が促進する事、この MFG-E8 を介した貪食が、これまで貪食能を持つ事が知られていなかった、組織の線維化を担う、筋線維芽細胞という細胞群によって行われることを見出した (J Clin Invest 2017)。



澤本*班*

•新生児脳内の放射状グリアが再生の足場であることを発見し、これを模倣する人工足場を用いて神経細胞の再生促進と歩行機能の改善に成功した(Cell Stem Cell 2018)。脳内で新たに産生された神経細胞の傷害部への移動を促進することにより、脳梗塞後の神経機能が回復することを発見した (Sci Adv 2018)。

七田*班*

•脳梗塞後に起こる炎症は、細胞死に伴って放出される内因性炎症惹起因子（DAMPs）によって惹起される。DAMPs は、脳内に浸潤したマクロファージが発現する MSR1 や MARCO のようなスカベンジャー受容体によって細胞内に取り込まれて排除されることを見出した (Nat Med 2017)。